CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074645

Trade Name : NICOTINE TRANSDERMAL SYSTEM USP 7MG/DAY

Generic Name: Nicotine Transdermal System USP 7mg/day

Sponsor : Sano Corporation

Approval Date: October 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074645

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074645

APPROVAL LETTER

ANDAs 74-611 (14 mg/day)
74-612 (21 mg/day)
74-645 (7 mg/day)

OCT 20 1997

Sano Corporation
Attention: Diane Servello
3250 Commerce Parkway
Miramar, FL 33025

Dear Madam:

This is in reference to your abbreviated new drug applications dated January 20, 1995 (74-611 and 74-612), and March 9, 1995 (74-645), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nicotine Transdermal System, USP.

Reference is also made to your amendments submitted to each application dated July 31, 1996; April 25, May 9, July 15, August 29, September 2, and October 16, 1997. We also acknowledge your amendments dated April 21, April 25, and May 19, 1995; August 19, 1996; and June 4, June 18, June 19, July 2, and July 3, 1997 submitted to ANDA 74-612.

The listed drug product referenced in your applications is subject to periods of patent protection which expire on May 21, 2008, (patent 5,016,652) and January 23, 2005 (patent 4,597,961). Your applications contain Paragraph IV certifications to each patent under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(4)(B)(iii) of the Act provides that "approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received." You have notified FDA that Sano has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Sano within the statutory forty-five day period.

We have completed the review of these abbreviated applications and have concluded that the drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Nicotine Transdermal System, 7 mg/day, 14 mg/day, and 21 mg/day to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Habitrol 7 mg/day, 14 mg/day, and 21 mg/day, respectively, of Novartis Consumer Health, Inc.). Your drug release testing should be incorporated into the

stability and quality control programs using the same methods proposed in your applications.

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

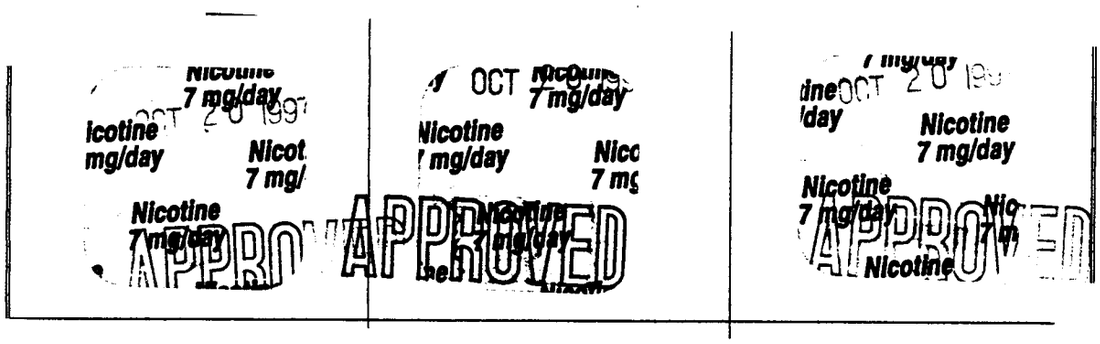
10/20/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074645

FINAL PRINTED LABELING


Nicotine
7 mg/day
OCT 20 1997
APPROVED
Nicotine
7 mg/day
APPROVED
Nicotine
7 mg/day
APPROVED

12

Nicotine
Transdermal
System
7
mg/day
Contents: APPROVED
14 Transdermal
Systems
One 9.7 cm² system
which contains
15.8 mg of nicotine.
Caution: Federal law
prohibits dispensing
without prescription.
FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.
3215-1234-14
Inactive Components:
Silicone adhesive, acrylate
adhesive, and aluminized
polyester.
Manufactured by:
Suno Corporation
Miramar, FL 33025

Nicotine
Transdermal
System
7
mg/day
Contents:14 Transdermal Systems
For Transdermal Use Only

Dosage & Administration:
Follow dosing instructions as directed by your physician. For application, see patient instructions.

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.

Storage:*Do not store above 30°C (86°F).*

See patient instructions for disposal information.

Contains NICOTINE, the addictive agent in cigarettes.

See bottom panel for lot number and expiration date.

Nicotine Transdermal System

Contents: 14 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

7 mg/day

One 9.7 cm² system which contains 15.8 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

Inactive Components:
Silicone adhesive, acrylate adhesive, and aluminized polyester.

Manufactured by:
Sano Corporation
Miramar, FL 33025

3 3215-1234-30 1

Nicotine Transdermal System

APPROVE

Contents:
30 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

7
mg/day

One 9.7 cm² system which contains 15.8 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

Dosage & Administration:
Follow dosing instructions as directed by your physician. For application, see patient instructions.

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.

Storage:*Do not store above 30°C (86°F).*

See patient instructions for disposal information.

Contains NICOTINE, the addictive agent in cigarettes.

See bottom panel for lot number and expiration date.

Nicotine Transdermal System

Contents: 30 Transdermal Systems

FOR TRANSDERMAL USE ONLY
DO NOT USE IF SEAL ON POUCH IS BROKEN
WARNING: KEEP OUT OF REACH OF CHILDREN.

7 mg/day

One 9.7 cm² system which contains 15.8 mg of nicotine.

Caution: Federal law prohibits dispensing without prescription.

NICOTINE TRANSDERMAL SYSTEM 7 mg/day

PRIMARY CONTAINER

FRONT

Nicotine Transdermal System

7 mg/day

FOR TRANSDERMAL USE ONLY

DO NOT USE IF SEAL ON POUCH IS BROKEN

WARNING: KEEP OUT OF REACH OF CHILDREN

ZL005 09/95

One 9.7cm² system which contains 15.8 mg of nicotine

Caution: *Federal law prohibits dispensing without prescription.*

APPROVED

BACK

OCT 20 1997

Contents: 1 System

Dosage & Administration: Follow dosing instructions as directed by your physician. For application see patient instructions

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH

Storage: Do not store above 30°C (86°F)

See patient instructions for disposal information. Contains NICOTINE, the addictive agent in cigarettes

Inactive Components: Silicone adhesive, acrylate adhesive, and aluminized polyester

Manufactured by:
SANO CORPORATION
Miramar, FL 33025

ZL014 09/95

APPROVED

FRONT

Nicotine Transdermal System

7 mg/day

FOR TRANSDERMAL USE ONLY

DO NOT USE IF SEAL ON POUCH IS BROKEN

WARNING: KEEP OUT OF REACH OF CHILDREN

ZL005 09/95

One 9.7cm² system which contains 15.8 mg of nicotine.

Caution: *Federal law prohibits dispensing without prescription.*

APPROVED

BACK

Contents: 1 System

OCT 20 1997

Dosage & Administration: Follow dosing instructions as directed by your physician. For application see patient instructions

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH

Storage: Do not store above 30°C (86°F)

See patient instructions for disposal information. Contains NICOTINE, the addictive agent in cigarettes

Inactive Components: Silicone adhesive, acrylate adhesive, and aluminized polyester

Manufactured by:
SANO CORPORATION
Miramar, FL 33025

ZL014 09/95

APPROVED

FRONT

Nicotine Transdermal System

7 mg/day

FOR TRANSDERMAL USE ONLY

DO NOT USE IF SEAL ON POUCH IS BROKEN

WARNING: KEEP OUT OF REACH OF CHILDREN

ZL005 09/95

One 9.7cm² system which contains 15.8 mg of nicotine.

Caution: *Federal law prohibits dispensing without prescription.*

APPROVED

BACK

OCT 20 1997

Contents: 1 System

Dosage & Administration: Follow dosing instructions as directed by your physician. For application see patient instructions

APPLY IMMEDIATELY UPON REMOVAL FROM POUCH

Storage: Do not store above 30°C (86°F)

See patient instructions for disposal information. Contains NICOTINE, the addictive agent in cigarettes

Inactive Components: Silicone adhesive, acrylate adhesive, and aluminized polyester

Manufactured by:
SANO CORPORATION
Miramar, FL 33025

ZL014 09/95

APPROVED

OCT 20 [illegible]

APPROVED

Nicotine Transdermal System USP

ZL00700A

Nicotine Transdermal System USP

Systemic delivery of 21, 14, or 7 mg/day over 24 hours

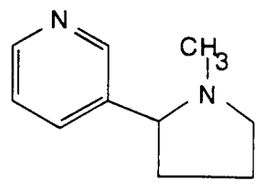
Prescribing Information

DESCRIPTION

Nicotine Transdermal System (Nicotine TDS) provides systemic delivery of nicotine following its application to intact skin for 24 hours.

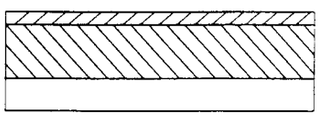
Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, S(-)-nicotine is the more active and is the more prevalent form in tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.

Structural Formula



Chemical Name:S-3-(1-methyl-2-pyrrolidinyl)pyridine
Molecular Formula: $C_{10}H_{14}N_2$
Molecular Weight: 162.23
Ionization Constants: pK_{a1}=7.84,pK_{a2}=3.04
Octanol-Water Partition Coefficient: 15:1 at pH 7

The Nicotine Transdermal Systems are pink opaque, flat (0.4 mm thick) square with round corners, multi-layer units containing nicotine as the active agent. The transdermal unit consists of: 1. An outer backing layer composed of a laminated aluminized polyester film; 2. A middle layer containing a silicone adhesive layer, an acrylate layer, and nicotine; and 3. A protective liner that covers the middle layer and must be removed prior to use.



Nicotine is the active ingredient; other components of the system are pharmacologically inactive.

The amount of nicotine delivered to the patient from each system (29 mcg/cm^2-h) is nearly proportional to the surface area. About 55% of the total amount of nicotine remains in the system 24 hours after application. Nicotine Transdermal Systems are labeled as to the dose actually absorbed by the patient. The dose of nicotine absorbed from a Nicotine Transdermal System represents 98% of the amount released from the system in 24 hours.

Dose Absorbed in 24 hours (mg/day)	System Surface Area (cm^2)	Total Nicotine Content (mg)
21	29.0	47.3
14	19.3	31.5
7	9.7	15.8

This product meets USP Drug Release Test 2 in the USP monograph for Nicotine Transdermal System.

CLINICAL PHARMACOLOGY

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect, exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), however, not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms such as cigarette craving can be reduced in some individuals by plasma nicotine levels lower than those from smoking.

Withdrawal from nicotine in addicted individuals is characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterized by nausea, abdominal pain, vomiting,

diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respirations and hypotension.

The cardiovascular effects of Nicotine 14 mg/day Transdermal Systems used continuously for 24 hours were compared with smoking every hour during waking hours, for 10 days. A small increase in blood pressure was detectable on the first day but not after 10 days. Heart rate was increased by 3%-7% and stroke volume decreased by 5%-12% on the 10th day of application. Nicotine transdermal treatment had no significant influence on cutaneous blood flow or skin temperature.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during Nicotine Transdermal therapy and/or smoking cessation (see PRECAUTIONS, Drug Interactions).

Pharmacokinetics

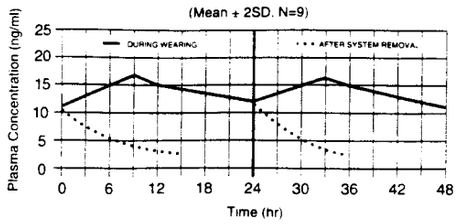
The volume of distribution following IV administration of nicotine is approximately 2 to 3 L/kg and the half-life ranges from 1 to 2 hours. The major eliminating organ is the liver, and average plasma clearance is about 1.2 L/min; the kidney and lung also metabolize nicotine. There is no significant skin metabolism of nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15-20 hours and concentrations that exceed nicotine by 10-fold.

Plasma protein binding of nicotine is <5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant consequences.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with high urine flow rates and urine acidification below pH 5.

The pharmacokinetic model which best fits the plasma nicotine concentrations from Nicotine Transdermal Systems is an open two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment. The nicotine from the drug matrix is released slowly from the system. Therefore, the decline of plasma nicotine concentrations during the last 12 hours is determined primarily by release of nicotine from the system through the skin.

Steady-State Plasma Nicotine Concentrations for Two Consecutive Applications of Nicotine TDS 21 mg/day
(Mean + 2SD, N=9)



Following an initial lag time of 1-2 hours, nicotine concentrations increase to a broad peak between 6 and 12 hours and then decrease gradually. Steady state for nicotine is attained within 2 days of initiating Nicotine Transdermal treatment and average plasma nicotine concentrations are, on average, 25% higher compared to single dose applications. Upon application of a new system and removal of the old system there is, in some patients, a slight and transient (30-60 min) increase in nicotine plasma concentration and its variability. Plasma nicotine concentrations are proportional to dose (i.e., linear kinetics are observed) for the three dosages of Nicotine Transdermal Systems. Nicotine kinetics are similar for all sites of application on the back, abdomen, or side.

Following removal of Nicotine Transdermal Systems, plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3-4 hours (see dotted line in graph) compared with 1-2 hours for IV administration, due to continued absorption from the skin depot. Most nonsmoking patients will have nondetectable nicotine concentrations in 10 to 12 hours.

Steady-State Nicotine Pharmacokinetic Parameters for Nicotine Transdermal Systems (mean, standard deviation, range)

Parameter	14 mg/day (N=9)			21 mg/day (N=9)		
(units)	Mean	SD	Range	Mean	SD	Range
C_{max}(ng/mL)	12	4	6-16	17	2	13-19
C_{avg}(ng/mL)	9	3	5-12	13	2	9-17
C_{min}(ng/mL)	6	2	3-10	9	2	7-14
T_{max}(hrs)	5	3	0-8	6	3	2-9

C_{max}: maximum observed plasma concentration
C_{avg}: average plasma concentration
C_{min}: minimum observed plasma concentration
T_{max}: time of maximum plasma concentration

Clinical Studies

The efficacy of Nicotine Transdermal treatment as an aid to smoking cessation was demonstrated in three placebo-controlled, double-blind trials in otherwise healthy patients smoking at least one pack per day (N=792). In two of the trials Nicotine Transdermal therapy was combined with concomitant support and in one trial nicotine transdermal was used without concomitant support. In all three trials, patients were treated for 7 weeks (3 weeks of titration and 4 weeks of maintenance) followed by 3 weeks of weaning. Quitting was defined as total abstinence from smoking as measured by patient diary and verified by expired carbon monoxide. The "quit rates" are the proportions of all persons initially enrolled who abstained after week 3.

The two trials in otherwise healthy smokers with concomitant support showed that Nicotine Transdermal therapy was more effective than placebo after 7 weeks. Quit rates were statistically significantly different after the additional 3-week weaning period. The quit rates varied approximately 3-fold among clinics for each treatment when a Nicotine Transdermal therapy was used with a concomitant support program. Data from these two studies (N=516) are combined in the Quit Rate table. Greater variability and decreased quit rates were demonstrated in both placebo and Nicotine Transdermal treatment groups when concomitant support was not employed (N=276, see table).

Quit Rates After Week 3 by Treatment

Concomitant Support	Treatment	Number of Patients	After 7 Weeks (range)	After Weaning (range)
Yes*	Nicotine TDS	260	19-54%	8-43%
	Placebo+	256	9-30%	8-30%
No**	Nicotine TDS	141	4-28%	4-20%
	Placebo+	135	0-24%	0-22%

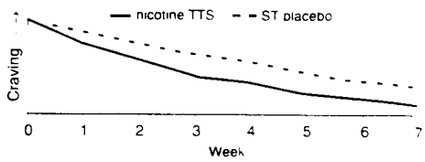
* Sub Therapeutic (ST) Placebo systems contained 13% of the nicotine found in respective-sized active system to allow blinding as to color and odor.

\+ Two trials with 9 clinics, number of patients per treatment ranged from 44 to 76.

\++ One trial with 5 clinics, number of patients per treatment ranged from 49 to 77.

Patients who used Nicotine TDS treatment in clinical trials had a significant reduction in craving for cigarettes, a major nicotine withdrawal symptom, as compared to placebo-treated patients (see graph). Reduction in craving, as with quit rate, is quite variable. This variability is presumed to be due to inherent differences in patient populations, e.g., patient motivation, concomitant illnesses, number of cigarettes smoked per day; number of years smoking, exposure to other smokers, socioeconomic status, etc., as well as differences among the clinics.

Severity of Craving by Treatment in the Two Clinical Trials with Concurrent Group Therapy (N=427)



Patients using Nicotine Transdermal Systems dropped out of the trials less frequently than did patients receiving placebo. Quit rates for the 32 patients over age 60 were comparable to the quit rates for the 369 patients aged 60 and under.

Individualization of Dosage

It is important to make sure that patients read the instructions made available to them and have their questions answered. They should clearly understand the directions for applying and disposing of Nicotine Transdermal Systems. They should be instructed to stop smoking completely when the first system is applied.

The success or failure of smoking cessation depends heavily on the quality, intensity, and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of Nicotine TDS therapy is complete abstinence. Significant health benefits have not been demonstrated for reduction of smoking. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued. Patients who have not stopped smoking after 4 weeks of Nicotine TDS therapy are unlikely to quit on that attempt.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled to determine why they failed. Patients should then probably be given a "therapy holiday" before the next attempt. A new quit attempt should be encouraged when the factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to assign their initial Nicotine TDS dosage using the recommended dosing schedule (see Dosing Schedule below). The need for dose adjustment should be assessed during the first 2 weeks. Patients should continue the dose selected with counseling and support over the following month. Those who have successfully stopped smoking during that time should be supported during 4 to 8 weeks of weaning after which treatment should be terminated.

Therapy should generally begin with the Nicotine TDS 21 mg/day dose (see Dosing Schedule below) except if the patient is small (less than 100 lbs), is a light smoker (less than 1/2 pack of cigarettes per day) or has cardiovascular disease.

Dosing Schedule

	Otherwise Healthy Patients	Other Patients*
Initial/Starting Dose	21 mg/day	14 mg/day
Duration of Treatment	4-8 weeks	4-8 weeks
First Weaning Dose	14 mg/day	7 mg/day
Duration of Treatment	2-4 weeks	2-4 weeks
Second Weaning Dose	7 mg/day	
Duration of Treatment	2-4 weeks	

* small patient (less than 100 lbs)
or light smoker (less than 10 cigarettes/day)
or patient with cardiovascular disease

The symptoms of nicotine withdrawal and excess overlap (see CLINICAL PHARMACOLOGY, Pharmacodynamics and ADVERSE REACTIONS). Since patients using Nicotine Transdermal treatment may also smoke intermittently, it may be difficult to determine if patients are experiencing nicotine withdrawal or nicotine excess.

The controlled clinical trials using Nicotine TDS therapy suggest that abnormal dreams are more often symptoms of nicotine excess while flatulence, anxiety, and depression are more often symptoms of nicotine withdrawal.

INDICATIONS AND USAGE

Nicotine Trandermal System is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Nicotine TDS treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Nicotine Transdermal Systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of Nicotine TDS systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Nicotine Transdermal Systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Nicotine TDS treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Nicotine Transdermal Systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Nicotine TDS therapy is used during pregnancy, or if the patient becomes pregnant while using Nicotine TDS treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Nicotine transdermal systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Nicotine TDS systems out of the reach of children and pets.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating nicotine TDS therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Nicotine transdermal systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the nicotine TDS dose should be reduced or Nicotine TDS treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Nicotine Transdermal Systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 6-week, open-label dermal irritation and sensitization study of Nicotine Transdermal Systems, 22 of 220 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Nicotine TDS treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease: Nicotine TDS systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Nicotine TDS treatment was reported occasionally. If serious cardiovascular symptoms occur with Nicotine TDS treatment, it should be discontinued.

Nicotine TDS treatment should generally not be used in patients during the immediate postmyocardial infarction period, patients with the serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Nicotine TDS treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Nicotine TDS treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Nicotine TDS treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients

A patient instruction sheet is included in the package of Nicotine Transdermal Systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Nicotine Transdermal Systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	**Possible Mechanism**
Acetaminophen, caffeine imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation
May Require an Increase in Dose at Cessation of Smoking	**Possible Mechanism**
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy: ***Pregnancy Category D:*** (See WARNINGS)

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, and increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Nicotine TDS treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Nicotine TDS treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birth-weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Nicotine TDS treatment has not been studied in pregnant humans.

Labor and Delivery

Nicotine transdermal systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother of the fetus during labor are unknown.

Nursing Mothers

Caution should be exercised when Nicotine TDS therapy is administered to nursing women. The safety of Nicotine TDS treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Nicotine TDS treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Nicotine Transdermal Systems should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from Nicotine transdermal systems alone or in combination with continued smoking.

Pediatric Use

Nicotine transdermal systems are not recommended for use in pediatric patients because the safety and effectiveness of Nicotine TDS treatment in pediatric patients who smoke have not been evaluated.

Geriatric Use

Forty-eight patients over the age of 60 participated in clinical trials of Nicotine TDS therapy. Nicotine TDS therapy appeared to be as effective in this age group as in younger smokers.

ADVERSE REACTIONS

Assessment of adverse events in the 792 patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both are confounded by concurrent smoking by many of the patients. In the trials, when reporting adverse events, the investigators did not attempt to identify the cause of the symptom.

Topical Adverse Events

The most common adverse event associated with topical nicotine is a short-lived erythema, pruritus, or burning at the application site, which was seen at least once in 35% of patients on Nicotine TDS treatment in the clinical trials. Local erythema after system removal was noted at least once in 17% of patients and local edema in 4%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 2% of patients on Nicotine TDS treatment (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related

The following adverse events were reported more frequently in Nicotine TDS-treated patients than in placebo-treated patients or exhibited a dose response in clinical trials.

Digestive system -- Diarrhea*, dyspepsia*.
Mouth/Tooth disorders -- Dry mouth.
Musculoskeletal system -- Arthralgia*, myalgia*.
Nervous system -- Abnormal dreams+, somnolence+.

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
+Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

Causal Relationship Unknown

Adverse events reported in Nicotine TDS- and placebo-treated patients at about the same frequency in clinical trials are listed below. The clinical significance of the association between Nicotine TDS treatment and these events is unknown, but they are reported as alerting information for the clinician.

Body as a whole -- Allergy+, back pain+.
Cardiovascular system -- Hypertension+.
Digestive system -- Abdominal pain+, constipation+, nausea*, vomiting.
Nervous system -- Dizziness*, concentration impaired+, headache (17%), insomnia*.
Respiratory system -- Cough increased+, pharyngitis+, sinusitis+
Urogenital system -- Dysmenorrhea*.

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
+Reported in 1% to 3% of patients.
Unmarked if reported in <1% of patients.

DRUG ABUSE AND DEPENDENCE

Nicotine Transdermal Systems are likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e., once daily).

Dependence on nicotine polacrilex chewing gum replacement therapy has been reported. Such dependence might also occur from transference to Nicotine Transdermal Systems of tobacco-based nicotine dependence. The use of the system beyond 3 months has not been evaluated and should be discouraged.

To minimize the risk of dependence, patients should be encouraged to withdraw gradually from Nicotine TDS treatment after 4 to 8 weeks of usage. Recommended dose reduction is to progressively decrease the dose every 2 to 4 weeks (see DOSAGE AND ADMINISTRATION).

OVERDOSAGE

The effects of applying several Nicotine Transdermal Systems simultaneously or of swallowing nicotine transdermal systems are unknown (see WARNINGS, Safety Note Concerning Children).

The oral LD_{50} for nicotine in rodents varies with species but is in excess of 24 mg/kg; death is due to respiratory paralysis. The oral minimum lethal dose of nicotine in dogs is greater than 5 mg/kg. The oral minimum acute lethal dose for nicotine in human adults is reported to be 40 to 60 mg (<1 mg/kg).

Two or three Nicotine Transdermal 30 cm^2 Systems in capsules fed to dogs weighing 8-17 kg were emetic, but did not produce any other significant clinical signs. The administration of these patches corresponds to about 6-17 mg/kg of nicotine.

Signs and symptoms of an overdose of Nicotine Transdermal Systems would be expected to be the same as those of acute nicotine poisoning including pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion, and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses. Lethal doses produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure.

Overdose From Topical Exposure

The Nicotine Transdermal System should be removed immediately if the patient shows signs of overdosage and the patient should seek immediate medical care. The skin surface may be flushed with water and dried. No soap should be used since it may increase nicotine absorption. Nicotine will continue to be delivered into the bloodstream for several hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics) after removal of the system because of a depot of nicotine in the skin.

Overdose From Ingestion

Persons ingesting nicotine transdermal systems should be referred to a health care facility for management. Due to the possibility of nicotine-induced seizures, activated charcoal should be administered. In unconscious patients with a secure airway, instill activated charcoal via nasogastric tube. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the system. Repeated doses of activated charcoal should be administered as long as the system remains in the gastrointestinal tract since it will continue to release nicotine for many hours.

Management of Nicotine Poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

Patients must desire to stop smoking and should be instructed to *stop smoking immediately* as they begin using Nicotine TDS therapy. The patient should read the patient instruction sheet on Nicotine TDS treatment and be encouraged to ask any questions. Treatment should be initiated with Nicotine TDS 21 mg/day or 14 mg/day systems (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

Once the appropriate dosage is selected the patient should begin 4-6 weeks of therapy at that dosage. The patient should stop smoking cigarettes completely during this period. If the patient is unable to stop cigarette smoking within 4 weeks, Nicotine TDS therapy should probably be stopped, since few additional patients in clinical trials were able to quit after this time.

Recommended Dosing Schedule for Healthy Patients[a]

(see CLINICAL PHARMACOLOGY, Individualization of Dosage)

Dose	Duration
Nicotine TDS 21 mg/day	First 6 Weeks
Nicotine TDS 14 mg/day	Next 2 Weeks[b]
Nicotine TDS 7 mg/day	Last 2 Weeks[c]

[a] Start with Nicotine TDS 14 mg/day for 6 weeks for patients who:
- have cardiovascular disease
- weigh less than 100 pounds
- smoke less than 1/2 a pack of cigarettes/day

Decrease dose to Nicotine TDS 7 mg/day for the final 2-4 weeks.

[b] Patients who have successfully abstained from smoking should have their dose of Nicotine TDS reduced after each 2-4 weeks of treatment until the 7 mg/day dose has been used for 2-4 weeks (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

[c] The entire course of nicotine substitution and gradual withdrawal should take 8-12 weeks, depending on the size of the initial dose. The use of Nicotine TDS beyond 3 months has not been studied.

The Nicotine Transdermal System should be applied promptly upon its removal from the protective pouch to prevent evaporative loss of nicotine from the system. Nicotine Transdermal Systems should be used only when the pouch is intact to assure that the product has not been tampered with.

Nicotine Transdermal Systems should be applied only once a day to a non-hairy, clean, and dry skin site on the trunk or upper, outer arm. After 24 hours, the used Nicotine TDS system should be removed and a new system applied to an alternate skin site. Skin sites should not be reused for at least a week. Patients should be cautioned not to continue to use the same system for more than 24 hours.

Safety and Handling

Nicotine Transdermal Systems can be a dermal irritant and can cause contact sensitization. Although exposure of health care workers to nicotine from Nicotine Transdermal Systems should be minimal, care should be taken to avoid unnecessary contact with active systems. If you do handle active systems, wash with water alone, since soap may increase nicotine absorption. Do not touch your eyes.

Disposal

When the used system is removed from the skin, it should be folded over and placed in the protective pouch which contained the new system. The used system should be immediately disposed of in such a way to prevent its access by children or pets. See patient information for further directions for handling and disposal.

HOW SUPPLIED

Nicotine Transdermal Systems are available as follows:

Nicotine Delivery Rate *(in vivo)*	Nicotine in System	System Size	Package Size	NDC Number
21 mg/day	47.3 mg	29.0 cm^2	30 systems	3215-1236-30
21 mg/day	47.3 mg	29.0 cm^2	14 systems	3215-1236-14

The patch is opaque tan, with a Nicotine 21 mg/day random all over brown print. The label is color coded with purple markings.

14 mg/day	31.5 mg	19.3 cm²	30 systems	3215-1235-30
14 mg/day	31.5 mg	19.3 cm²	14 systems	3215-1235-14

The patch is opaque tan, with a Nicotine 14 mg/day random all over brown print. The label is color coded with pink markings.

7 mg/day	15.8 mg	9.7 cm²	30 systems	3215-1234-30
7 mg/day	15.8 mg	9.7 cm²	14 systems	3215-1234-14

The patch is opaque tan, with a Nicotine 7 mg/day random all over brown print. The label is color coded with yellow markings.

How to Store

Do not store above 86°F (30°C) because Nicotine transdermal systems are sensitive to heat. A slight discoloration of the system is not significant.

Do not store unpouched. Once removed from the protective pouch, Nicotine TDS systems should be applied promptly since nicotine is volatile and the system may lose strength.

CAUTION: Federal law prohibits dispensing without prescription.

ZL00700A Rev. 01/97 Printed in U.S.A.

Manufactured by:

Sano Corporation

Miramar, Florida 33025

Nicotine Transdermal System USP

Patient Instructions

IMPORTANT

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. Nicotine can be [illegible] and harmful. Small amounts of nicotine can cause serious illness in children. Even used nicotine patches contain enough nicotine to poison children and pets. Be sure to throw nicotine patches away out of the reach of children and pets. If a child puts on nicotine patches or plays with a nicotine patch that is out of the sealed pouch, take it away from the child and contact a poison control center, or contact a doctor immediately.

Women: Nicotine in any form may cause harm to your unborn baby. If you use nicotine while you are pregnant: Do not use nicotine patches if you are pregnant or nursing unless advised by your doctor. If you become pregnant while using nicotine patches or if you think you might be pregnant, stop smoking and don't use nicotine transdermal systems until you have talked to your doctor.

This leaflet will provide you with general information about nicotine and specific instructions about how to use nicotine patches. It is important that you read it carefully and completely before you start using nicotine patches. Be sure to read the PRECAUTIONS section before using nicotine transdermal systems because, as with all drugs, nicotine transdermal system treatment has side effects. Since this leaflet is only a summary of information, be sure to ask your doctor if you have any question or want to know more.

INTRODUCTION

IT IS IMPORTANT THAT YOU ARE FIRMLY COMMITTED TO GIVING UP SMOKING.

Nicotine transdermal system is a skin patch containing nicotine designed to help you quit smoking cigarettes. When you wear a nicotine patch, it releases nicotine through the skin into your bloodstream while you're wearing it. The nicotine which is in your skin will still be entering your bloodstream for several hours after you take the patch off.

It is the nicotine in cigarettes that causes addiction to smoking. Nicotine transdermal system therapy replaces some of the nicotine you crave when you are stopping smoking. Nicotine patches may also help relieve other symptoms of nicotine withdrawal that may occur when you stop smoking such as irritability, frustration, anger, anxiety, difficulty in concentration, and restlessness.

There are three doses of nicotine transdermal systems. Your doctor has chosen the nicotine transdermal system with the correct dose for you and may adjust it during the first week or two. After about 6 weeks, your doctor will give you smaller nicotine patches approximately every two weeks. The smaller patches give you less nicotine. In time, you will be completely off nicotine.

INFORMATION ABOUT NICOTINE PATCHES

How Nicotine Patches Work

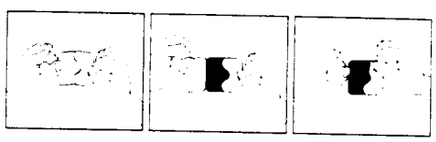
Nicotine patches contain nicotine. When you put a nicotine transdermal system on your skin, nicotine passes from the patch through the skin and into your blood.

How to Apply a Nicotine Patch

Step 1. Choose a non-hairy, clean, dry area of your body or the upper, outer part of your arm. Do not put a nicotine patch on skin that is very oily, burned, broken out, cut, or irritated in any way.

Step 2. Do not remove the nicotine patch from its sealed protective pouch until you are ready to use it. Carefully tear open the pouch. Discard the used patch you take off by folding it in half and putting it into the opened pouch. Throw it away in the trash out of the reach of children and pets (see Step 7).

Step 3. A white protective liner covers the sticky side of the nicotine patch the side that will be put on your skin. The liner has a precut slit to help you remove it from the patch. With the white side facing you, fold the unit back along the pre-cut slit, and then pull the liner away from the nicotine patch starting at the pre-cut slit. Hold the nicotine patch at the edge (touch the sticky side as little as possible) and pull off the other piece of the protective liner. Throw away this liner.



Step 4. Immediately apply the sticky side of the nicotine patch to your skin. Press the nicotine patch firmly on your skin with the palm of your hand for about 10 seconds. Make sure it sticks well to your skin, especially arounds the edges.

Step 5. Wash your hands when you have finished applying the nicotine patch. Nicotine on your hands could get into your eyes and nose and could cause stinging, redness, or more serious problems.

Step 6. After approximately 24 hours, remove the patch you have been wearing. Choose a *different* place on your skin to apply the next nicotine patch and repeat Steps 1 to 5. Do not return to a previously used skin site for at least one week. Do not leave on the nicotine patch for more than 24 hours because it may irritate your skin and because it loses strength after 24 hours.

Nicotine Transdermal System USP

Nicotine Transdermal System USP

Patient Instructions

IMPORTANT

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. Nicotine can be very toxic and harmful. Small amounts of nicotine can cause serious illness in children. Even used nicotine patches contain enough nicotine to poison children and pets. Be sure to throw nicotine patches away out of reach of children and pets. If a child puts on nicotine patches or plays with a nicotine patch that is out of the sealed pouch, take it away from the child and contact a poison control center, or contact a doctor immediately.

Women: Nicotine in any form may cause harm to your unborn baby if you use nicotine while you are pregnant. Do not use nicotine patches if you are pregnant or nursing unless advised by your doctor. If you become pregnant while using nicotine patches or if you think you might be pregnant, stop smoking and don't use nicotine transdermal systems until you have talked to your doctor.

This leaflet will provide you with general information about nicotine and specific instruction about how to use nicotine patches. It is important that you read it carefully and completely before you start using nicotine patches. Be sure to read the PRECAUTIONS section before using nicotine transdermal systems because, as with all drugs, nicotine transdermal system treatment has side effects. Since this leaflet is only a summary of information, be sure to ask your doctor if you have any question or want to know more.

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It is the nicotine in cigarettes that causes addiction to smoking. Nicotine transdermal system therapy replaces some of the nicotine you crave when you are stopping smoking. Nicotine patches

Nicotine transdermal system helps reduces some of the withdrawal symptoms you crave when you are stopping smoking. Nicotine patches may also help relieve other symptoms of nicotine withdrawal that may occur when you stop smoking such as irritability, frustration, anger, anxiety, difficulty in concentration, and restlessness.

There are three doses of nicotine transdermal systems. Your doctor has chosen the nicotine transdermal system with the correct dose for you and may adjust it during the first week or two. After about 6 weeks, your doctor will give you smaller nicotine patches approximately every two weeks. The smaller patches give you less nicotine. In time, you will be completely off nicotine.

INFORMATION ABOUT NICOTINE PATCHES

How Nicotine Patches Work

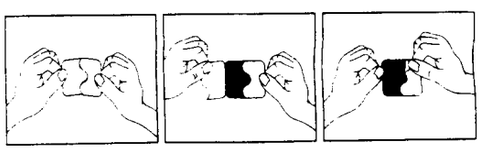
Nicotine patches contain nicotine. When you put a nicotine transdermal system on your skin, nicotine passes from the patch through the skin and into your blood.

How to Apply a Nicotine Patch

Step 1. Choose a non-hairy, clean, dry area of your body or the upper, outer part of your arm. Do not put a nicotine patch on skin that is very oily, burned, broken out, cut, or irritated in any way.

Step 2. Do not remove the nicotine patch from its sealed protective pouch until you are ready to use it. Carefully tear open the pouch. Discard the used patch you take off by folding it in half and putting it into the opened pouch. Throw it away in the trash out of the reach of children and pets (see Step 7).

Step 3. A white protective liner covers the sticky side of the nicotine patch the side that will be put on your skin. The liner has a precut slit to help you remove it from the patch. With the white side facing you, fold the unit back along the pre-cut slit, and then pull the liner away from the nicotine patch starting at the pre-cut slit. *Hold the nicotine patch* at the edge (touch the sticky side as little as possible) and pull off the other piece of the protective liner. Throw away this liner.



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Step 5. Wash your hands when you have finished applying the nicotine patch. Nicotine on your hands could get into your eyes and nose and could cause stinging, redness, or more serious problems.

Step 6. After approximately 24 hours, remove the patch you have been wearing. Choose a *different* place on your skin to apply the next nicotine patch and repeat Steps 1 to 5. Do not return to a previously used skin site for at least one week. Do not leave on the nicotine patch for more than 24

sure it sticks well to your skin, especially arounds the edges

Step 5. Wash your hands when you have finished applying the nicotine patch. Nicotine on your hands could get into your eyes and nose and could cause stinging, redness, or more serious problems.

Step 6. After approximately 24 hours, remove the patch you have been wearing. Choose a *different* place on your skin to apply the next nicotine patch and repeat Steps 1 to 5. Do not return to a previously used skin site for at least one week. Do not leave on the nicotine patch for more than 24 hours because it may irritate your skin and because it loses strength after 24 hours.

Step 7. Fold the used nicotine patch in half with the sticky side together. After you have put on a new nicotine patch, take its pouch and place the used, folded nicotine patch inside of it. Throw the pouch in the trash away from children and pets.

When to Apply a Nicotine Patch

If you apply the nicotine patch at about the same time each day, it will help you to remember when to put on a new nicotine patch. If you want to change the time when you put on your patch, you can do so. Just remove the nicotine patch you are wearing and put on a new one. After that, apply the nicotine patch at the new time each day.

If Your Nicotine Patch Gets Wet

Water will not harm the nicotine patch you are wearing. You can bathe, swim, use a hot tub, or shower while you are wearing a nicotine patch.

If Your Nicotine Patch Comes Off

If your nicotine patch falls off, put on a new one. Remove the nicotine patch at your regular time to keep your schedule the same, or 24 hours after applying the replacement patch if you wish to change the time each day that you apply a new patch. Before putting on a new patch, make sure you select a non-hairy area which is not irritated and is clean and dry.

Disposing of a Nicotine Patch

Fold the used nicotine patch in half with the sticky side together. After you put on a new nicotine patch, take its opened pouch of aluminum foil and place the used, folded nicotine patch inside of it. THROW THE POUCH IN THE TRASH AWAY FROM CHILDREN AND PETS.

Storage Instructions

Keep the nicotine patch in its protective pouch until you are ready to use it. Do not store your nicotine patches above 86°F (30°C) because the patch is sensitive to heat. Remember, the inside of your car can reach temperatures much higher than this in the summer.

PRECAUTIONS

What to Ask Your Doctor

Ask your doctor about possible problems with nicotine transdermal system therapy. Be sure to tell your doctor if you have had any of the following:

- a recent heart attack (myocardial infarction)
- irregular heart beat (arrhythmia)
- severe or worsening heart pain (angina pectoris)
- allergies to drugs
- rashes from adhesive tape or bandages
- skin diseases
- very high blood pressure
- stomach ulcers
- overactive thyroid
- diabetes requiring insulin
- kidney or liver disease

If You Are Taking Medicines

Nicotine patch use, together with stopping smoking, may change the effect of other medicines. It is important to tell your doctor about all the medicines you are taking.

What to Watch For (Adverse Effects)

You should not smoke while using the nicotine patch. It is possible to get too much nicotine (an overdose), especially if you use a nicotine patch and smoke at the same time. Signs of an overdose would include bad headaches, dizziness, upset stomach, drooling, vomiting, diarrhea, cold sweat, blurred vision, difficulty with hearing, mental confusion and weakness. An overdose might cause you to faint.

If Your Skin Reacts to the Nicotine Patch

When you first put on a nicotine patch, mild itching, burning, or tingling is normal and should go away within an hour. After you remove a nicotine patch, the skin under the patch might be somewhat red. Your skin should not stay red for more than a day. If you get a skin rash after using a nicotine patch, or if the skin under the patch becomes swollen or very red, call your doctor. Do not put on a new patch. You may be allergic to one of the components of the nicotine patch.

If you do become allergic to the nicotine in the nicotine patch, you could get sick from using cigarettes or other nicotine-containing products.

What to Do When Problems Occur

IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROB-

You should not smoke while using the nicotine patch. It is possible to get too much nicotine (an overdose), especially if you use a nicotine patch and smoke at the same time. Signs of an overdose would include bad headaches, dizziness, upset stomach, drooling, vomiting, diarrhea, cold sweat, blurred vision, difficulty with hearing, mental confusion and weakness. An overdose might cause you to faint.

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If you do become allergic to the nicotine in the nicotine patch, you could get sick from using cigarettes or other nicotine-containing products.

What to Do When Problems Occur

IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROBLEMS, TAKE OFF THE NICOTINE PATCH AND CALL YOUR DOCTOR AT ONCE.

ZL00800A Rev. # 01/97 Printed in U.S.A.

Manufactured by:
Sano Corporation
Miramar, Fl. 33025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074645

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-645

3. NAME AND ADDRESS OF APPLICANT

Sano Corporation
Attention: D. Servello
3250 Commerce Parkway
Miramar, FL 33025

4. LEGAL BASIS for ANDA SUBMISSION

page 100007
Listed Drug: Habitrol™ Nicotine Transdermal System/Ciba Corporation
Patent#s 5016652 and 4597961 expire 5.21.2008 and 7.1.2003, respectively. Exclusivity expired 11.7.94.

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Nicotine Transdermal System

8. SUPPLEMENT(s) PROVIDE(s) FOR: None

9. AMENDMENTS AND OTHER DATES:

Applicant:

03.09.95: Original
04.13.95: Amendment (Debarment Certification)
04.24.95: Amendment (Notice of certification of noninfringement of patent#s 5016652 and 4597961
06.07.95: Correspondance
10.20.95: Amendment
11.01.95: Amendment
02.12.96: Amendment
06.04.96: Amendment
07.31.96: Amendment
08.14.96: Amendment
10.10.96: Amendment
02.12.97: Amendment **Subject of this review**
05.09.97: Amendment **Subject of this review**
08.28.97: Fax amendment **Subject of this review**
09.02.97: Fax amendment **Subject of this review**

DA:

4.6.95: Acknowledge receipt
08.16.95: NA letter #1
05.24.96: NA letter #2
01.14.97: NA letter #3
04.25.97: NA letter #4

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC

Relief of Nicotine Withdrawal R_x

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM 14. POTENCY

Transdermal Patch 7 mg/day

15. CHEMICAL NAME AND STRUCTURE

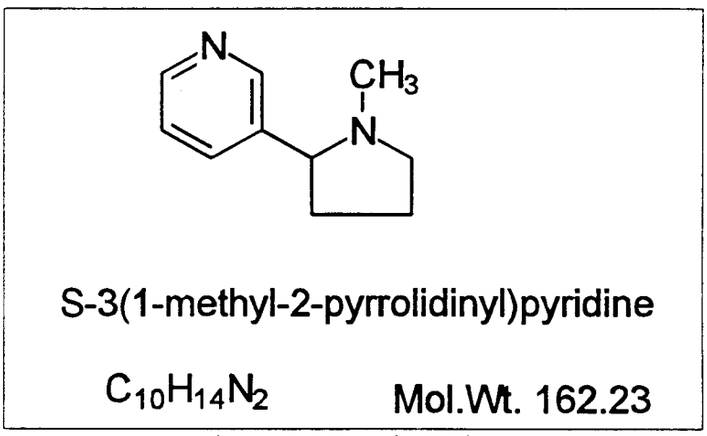

Figure 1: Nicotine

16. RECORDS AND REPORTS None

17. COMMENTS

a. The following DMFs are satisfactory:
b. The Chemistry, Manufacturing, and Controls are satisfactory.
c. Compendial drug substance and drug product. MV satisfactory, Southeast Regional Labs, 9.19.96.
d. EER submitted 4.3.96; satisfactory, 7.22.96; updates requested.

e. Professional labeling - Satisfactory, J. White, 3.18.97.
f. Bio-review satisfactory, per F. Nouravarsani, 08.28.97.
g. The skin irritation studies have been found satisfactory, M. M. Fanning, 7.25.97.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is satisfactory in chemistry, manufacturing and controls, labeling and bio-review. It may be approved.

19. REVIEWER: DATE COMPLETED:

U. V. Venkataram, Ph.D. 07.12.97, 09.02.97 (revised)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074645

BIOEQUIVALENCE REVIEW(S)

MAR 21 1997

Nicotine Transdermal System
7 mg/day
ANDA #74-645
Reviewer: F. Nouravarsani
74645W.796

Sano Corporation
Miramar, FL
Submission Date:
July 31, 1996

REVIEW OF A WAIVER REQUEST

Sano has requested a waiver of bioequivalence study requirements for its Test product, Nicotine Transdermal System, 7 mg/day.

The firm's bioequivalence study conducted on its higher strengh test product, Nicotine Transdermal System, 21 mg/day has been found incomplete. Therefore the firm should be informed that, this submission will not be reviewed at this time. The firm should resubmit a waiver request for its test product, Nicotine Transdermal System, 7 mg/day.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

for RM 3/12/97

Concur:_____ _____ Date: 3/27/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/03-07-97/74645W.796

CC: ANDA #74-645 (original, duplicate), Nouravarsani, HFD-658, Drug File, Division File

MAR 24 1997

Nicotine Transdermal System
7 mg/day
ANDA #74-645
Reviewer: F. Nouravarsani
74645DW.095

Sano Corporation
Miramar, FL
Submission Date:
October 20, 1995

REVIEW OF A DISSOLUTION TESTING AND A WAIVER REQUEST

Sano has requested a waiver of bioequivalence study requirements for its Test product, Nicotine Transdermal System, 7 mg/day.

The firm's bioequivalence study conducted on its higher strengh test product, Nicotine Transdermal System, 21 mg/day has been found incomplete. Therefore the firm should be informed that, this submission will not be reviewed at this time. The firm should resubmit a waiver request for its test product.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE for RH 3/12/97

Concur: _____ Date: 3/24/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/03-07-97/74645DW.095

CC: ANDA #74-645 (original, duplicate), Nouravarsani, HFD 658, Drug File, Division File

ANDA's 74-612 (21 mg/day)
74-611 (14 mg/day)
74-645 (7 mg/day)

SEP 23 '97

Sano Corporation
Attention: Diane Servello
3250 Commerce Parkway
Miramar, FL 33025

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Nicotine Transdermal Systems.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following drug release testing should be incorporated into your manufacturing controls and stability program. The test should be conducted in 500 mL of phosphate buffer at 32° C using USP 23 apparatus 6, 50 rpm. The test product should meet the following specifications:

   Amount dissolved at 6 hours: betwee
   Amount dissolved at 24 hours: bet

In addition, we have the following comment:

There was an error in calculation of the 90% CI. Furthermore, degrees of freedom (df) for sequence effect was reported 3 instead of 1 in statement reports of ANOVA for the parameters of multiple-dose at steady state.

However, the data were reanalyzed using SAS-GLM procedure, and the 90% CIs were recalculated for the AUCs and Cmax for both single and multiple dose studies. The 90% CIs fall in the required range by the Division of Bioequivalence.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research